Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03014425.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Europäisches Patentamt | European Patent Office | Office européen des brevets

Anmeldung Nr:
Application no.: 03014425.7
Demande no:

Anmeldetag:
Date of filing: 30.06.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ALTANA Pharma AG
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel use

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

Novel Use

Field of application of the invention

The invention relates to the use of a certain structure-element as an integral part of the overall structure of pyrrolodihydroisoquinoline compounds, which inhibit PDE10 and are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

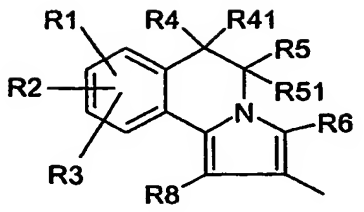
The International applications WO 02/48144, WO 03/014115, WO 03/014116 and WO 03/014117 disclose pyrrolodihydroisoquinoline derivatives with PDE10 inhibitory activity. Said International applications are incorporated by reference into the specification of the present invention in their entirety for all purposes.
The European application EP 1250923 discloses the use of selective PDE10 inhibitors in general, and papaverine in particular, for the treatment of certain neurologic and psychiatric disorders. Said European application is incorporated by reference into the specification of the present invention in its entirety for all purposes.

Description of the invention

It has now been found that the structure-element per se, which is specified in greater details below, as well as its use as integral part of the overall structure of compounds, which inhibit PDE10, differ profoundly from prior art. Thus, said novel structure-element differs from prior art by unanticipated, sophisticated and originative structural features and its inherent, surprising and particularly advantageous function as integral part of the overall structure of compounds which inhibit PDE10.

In a first aspect, the present invention provides structure-activity principles for use in the design of PDE10 inhibitors of the pyrrolodihydroisoquinoline class with surprising and particularly advantageous properties.
In a special aspect, the present invention provides structure-activity principles for use in the design of PDE10 inhibitors of the pyrrolodihydroisoquinoline class with improved effectiveness and/or improved selectivity.

Thus, a special object (special object a) of the present invention is the use of a structure-element of the formula X



(X)

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is hydrogen or 1-4C-alkyl,

R41 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen or 1-4C-alkyl,

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl,

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

A further special object (special object b) of the present invention is the use of a structure-element of the formula X,

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is 1-4C-alkyl,

R41 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkyl,

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl,

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is -C(O)-OR9, in which

R9 is 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

A further special object (special object c) of the present invention is the use of a structure-element of the formula X,

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy, or

R2 and R3 bound to the benzo ring moiety in ortho-position to each other together form a 1-2C-alkylenedioxy bridge, or

R2 and R3 bound to the benzo ring moiety in ortho-position to each other together form a completely or predominantly fluorine-substituted 1-2C-alkylenedioxy bridge, or

R1 and R2 bound to the benzo ring moiety in ortho-position to each other together form a 1-2C-alkylenedioxy bridge and R3 is hydrogen, or

R1 and R2 bound to the benzo ring moiety in ortho-position to each other together form a completely or predominantly fluorine-substituted 1-2C-alkylenedioxy bridge and R3 is hydrogen,

R4 is hydrogen,

R41 is hydrogen,

R5 is ethyl or, in particular, methyl,

R51 is hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is 1-4C-alkyl, phenyl, 2-4C-alkinyl, cyano, $-CH_2-O-R81$, phenylcarbonyl, -C(O)-N(R82)R83 or -C(O)-OR9, in which

R81 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4-alkyl or 1-4C-alkylcarbonyl,

R82 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, phenyl or phenyl-1-4C-alkyl,

R83 is hydrogen or 1-4C-alkyl, or

R82 and R83 together and with inclusion of the nitrogen atom, to which they are bound, form a heterocyclic ring radical selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl or N-(1-4C-alkyl)-piperazinyl,

R9 is hydrogen or 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

2-4C-Alkyl represents a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl radical.

1-6C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 6 carbon atoms. Examples which may be mentioned are the hexyl, isohexyl (4-methylpentyl), neohexyl (3,3-dimethylbutyl), pentyl, isopentyl (3-methylbutyl), neopentyl (2,2-dimethylpropyl), butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl or methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

2-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy radical.

3-7C-Cycloalkoxy represents cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy, of which cyclopropyloxy, cyclobutyloxy and cyclopentyloxy are preferred.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

3-7C-Cycloalkylmethoxy represents cyclopropylmethoxy, cyclobutylmethoxy, cyclopentylmethoxy, cyclohexylmethoxy and cycloheptylmethoxy, of which cyclopropylmethoxy, cyclobutylmethoxy and cyclopentylmethoxy are preferred.

3-7C-Cycloalkyl-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 3-7C-cycloalkyl radicals. Examples which may be mentioned are the cyclopropylmethyl, the cyclohexylethyl and the cyclohexylmethyl radicals.

As completely or predominantly fluorine-substituted 1-4C-alkoxy, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy, in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and preferably the difluoromethoxy radicals may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radicals are replaced by fluorine atoms.

1-4C-Alkoxy-2-4C-alkoxy represents one of the abovementioned 2-4C-alkoxy radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-methoxyethoxy, 2-ethoxyethoxy and the 2-isopropoxyethoxy radicals.

1-4C-Alkoxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the 2-methoxyethyl and the 2-isopropoxyethyl radicals.

1-2C-Alkylenedioxy represents, for example, the methylenedioxy [-O-CH_2-O-] and the ethylenedioxy [-O-CH_2-CH_2-O-] radicals.

As completely or predominantly fluorine-substituted 1-2C-alkylenedioxy bridge, for example, the difluoromethylenedioxy [-O-CF_2-O-] radical may be mentioned. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkylenedioxy radical are replaced by fluorine atoms.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by a phenyl radical. Examples which may be mentioned are the phenethyl and the benzyl radicals.

1-4C-Alkoxycarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxycarbonyl and ethoxycarbonyl radicals.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

3-4C-Alkylene is a straight-chain alkylene radical such as, for example, the trimethylene (-CH_2-CH_2-CH_2-) or the tetramethylene (-CH_2-CH_2-CH_2-CH_2-) radical.

Halogen within the meaning of the invention is bromine and, preferably, chlorine and fluorine.

Hydroxy-2-4C-alkyl stands for one of the abovementioned 2-4C-alkyl radicals which is substituted by a hydroxyl group. Examples which may be mentioned are the 2-hydroxyethyl and 3-hydroxypropyl radicals.

Amino-2-4C-alkyl stands for one of the abovementioned 2-4C-alkyl radicals which is substituted by an amino group. Examples which may be mentioned are the 2-aminoethyl and 3-aminopropyl radicals.

In addition to the nitrogen atom, mono- or di-1-4C-alkylamino radicals contain one or two of the abovementioned 1-4C-alkyl radicals. Di-1-4C-alkylamino is to be emphasized and here, in particular, dimethyl-, diethyl- and diisopropylamino.

2-4C-Alkinyl is a straight chain or branched alkinyl radical having 2 to 4 carbon atoms. Examples are the 2-propinyl (propargyl) and the ethinyl radicals.

Het1 refers to a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom. Examples for Het2 include e.g. piperidin-1-yl, 4-methyl-piperidin-1-yl, 4-hydroxypiperidin-1-yl, morpholin-4-yl, pyrrolidin-1-yl, piperazin-1-yl, imidazolidin-1-yl, thiomorpholin-4-yl, homopiperidin-1-yl, homopiperazin-1-yl, 4-N-(1-4C-alkyl)-homopiperazin-1-yl or piperazinyl substituted on a ring nitrogen atom by R613 [4-N-(R613)-piperazin-1-yl] such as, for example, 4-N-(1-4C-alkyl)-piperazin-1-yl, 4-N-(hydroxy-2-4C-alkyl)-piperazin-1-yl, 4-N-(dimethylamino-2-4C-alkyl)-piperazin-1-yl, 4-N-(3-6C-cycloalkyl)-piperazin-1-yl, 4-N-formyl-piperazin-1-yl, 4-N-(pyridin-4-yl)-piperazin-1-yl, 4-N-(pyrimidin-2-yl)-piperazin-1-yl or 4-N-(3-6C-cycloalkylmethyl)-piperazin-1-yl.

N-(1-4C-alkyl)-piperazinyl stands for the piperazin-1-yl radical substituted by one of the abovementioned 1-4C-alkyl radicals on the 4-N ring nitrogen atom.

A subobject (subobject a1) of the special object a according to this invention worthy to be mentioned is the use of a structure-element of the formula X,
in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,
R2 is 1-4C-alkoxy or halogen,
R3 is hydrogen or 1-4C-alkoxy,
R4 is hydrogen,
R41 is hydrogen,
R5 is ethyl or, in particular, methyl,
R51 is hydrogen,
R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which
R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which
R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,
R612 is hydrogen or 1-4C-alkyl, or
R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which
Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject a2) of the special object a according to this invention more worthy to be mentioned is the use of a structure-element of the formula X,

in which

R1 is halogen or 1-4C-alkoxy,

R2 is hydrogen, halogen or 1-4C-alkoxy,

R3 is 1-4C-alkoxy,

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen, methyl or ethyl,

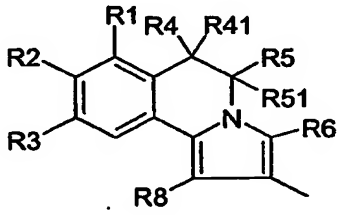
R51 is hydrogen,

R6 is methyl, ethyl or methoxycarbonylethyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject a3) of the special object a according to this invention in particular worthy to be mentioned is the use of a structure-element of the formula Xa



(Xa)

in which

R1 is hydrogen,

R2 is methoxy or ethoxy,

R3 is chlorine or fluorine,

or, as a first alternative,

R1 is hydrogen,

R2 is chlorine or fluorine,

R3 is methoxy or ethoxy,

or, as a second alternative,

R1 is hydrogen,

R2 is methoxy or ethoxy,

R3 is methoxy or ethoxy,

or, as a third alternative,
R1 is methoxy or ethoxy,
R2 is chlorine or fluorine,
R3 is methoxy or ethoxy,
or, as a fourth alternative,
R1 is chlorine or fluorine,
R2 is methoxy or ethoxy,
R3 is methoxy or ethoxy,
or, as a fifth alternative,
R1 is methoxy or ethoxy,
R2 is methoxy or ethoxy,
R3 is chlorine or fluorine,
or, as a sixth alternative,
R1 is methoxy or ethoxy,
R2 is methoxy or ethoxy,
R3 is methoxy or ethoxy,

R4 is hydrogen,
R41 is hydrogen,
R5 is ethyl or, in particular, methyl,
R51 is hydrogen,
R6 is methyl, ethyl or methoxycarbonylethyl,
R8 is cyano,
as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject a4) of the special object a according to this invention in more particular worthy to be mentioned is the use of a structure-element of the formula Xa,
in which
R1 is hydrogen,
R2 is methoxy,
R3 is methoxy,
R4 is hydrogen,
R41 is hydrogen,
R5 is methyl,
R51 is hydrogen,
R6 is methyl or methoxycarbonylethyl,
R8 is cyano,
as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject b1) of the special object b according to this invention worthy to be mentioned is the use of a structure-element of the formula X,
in which
R1 is halogen or 1-4C-alkoxy,
R2 is hydrogen, halogen or 1-4C-alkoxy,
R3 is 1-4C-alkoxy,
R4 is hydrogen,
R41 is hydrogen,
R5 is methyl or ethyl,
R51 is hydrogen,
R6 is methyl, ethyl or methoxycarbonylethyl,
R8 is -C(O)-OR9, in which
R9 is 1-4C-alkyl,
as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject b2) of the special object b according to this invention more worthy to be mentioned is the use of a structure-element of the formula Xa,
in which
R1 is hydrogen,
R2 is methoxy or ethoxy,
R3 is chlorine or fluorine,
or, as a first alternative,
R1 is hydrogen,
R2 is chlorine or fluorine,
R3 is methoxy or ethoxy,
or, as a second alternative,
R1 is hydrogen,
R2 is methoxy or ethoxy,
R3 is methoxy or ethoxy,
or, as a third alternative,
R1 is methoxy or ethoxy,
R2 is chlorine or fluorine,
R3 is methoxy or ethoxy,
or, as a fourth alternative,
R1 is chlorine or fluorine,
R2 is methoxy or ethoxy,
R3 is methoxy or ethoxy,
or, as a fifth alternative,
R1 is methoxy or ethoxy,

R2 is methoxy or ethoxy,
R3 is chlorine or fluorine,
or, as a sixth alternative,
R1 is methoxy or ethoxy,
R2 is methoxy or ethoxy,
R3 is methoxy or ethoxy,

R4 is hydrogen,
R41 is hydrogen,
R5 is ethyl or, in particular, methyl,
R51 is hydrogen,
R6 is methyl, ethyl or methoxycarbonylethyl,
R8 is -C(O)-OR9, in which
R9 is 1-4C-alkyl,
as integral part of the overall structure of compounds which inhibit PDE10.

A subobject (subobject b3) of the special object a according to this invention in particular worthy to be mentioned is the use of a structure-element of the formula Xa,
in which
R1 is hydrogen,
R2 is methoxy,
R3 is methoxy,
R4 is hydrogen,
R41 is hydrogen,
R5 is methyl,
R51 is hydrogen,
R6 is methyl or methoxycarbonylethyl,
R8 is -C(O)-OR9, in which
R9 is 1-4C-alkyl,
as integral part of the overall structure of compounds which inhibit PDE10.

Regarding the objects and subobjects according to the present invention, the subobjects a1, a2, a3 and a4 are to be emphasized.
The subobjects a2, a3 and a4 are in particular to be emphasized, and the subobjects a3 and, especially, a4 are in more particular to be emphasized.

A further object of the present invention is the use of a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, in particular in the subobjects thereto, in more particular in the subobjects emphasized above,

as an integral part of the overall structure of compounds, which inhibit effectively PDE10, for use in treating disorders of the central nervous system and/or, particularly, cancer.

A further object of the present invention is the use of a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, as an integral part of the overall structure of compounds for use in therapy.

A further object of the present invention is the use of a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, as an integral part of the overall structure of compounds, which inhibit PDE10, for use in the manufacture of pharmaceutical compositions.

A further object of the present invention is the use of a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, to provide compounds, which inhibit PDE10.

A further object of the present invention is a process to provide compounds, which inhibit PDE10, comprising the following steps:
a.) designing intellectually the structure of a compound comprising - as part of its overall structure - a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, in particular, in the subobjects thereto, in more particular in the subobjects emphasized above;
b.) synthesizing substantially a compound having said designed structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

A further object of the present invention is a compound obtainable by the abovementioned process to provide compounds, which inhibit PDE10.

A further object of the present invention are compounds which inhibit effectively PDE10 and which comprise a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, as an integral part of their overall structures.

Consequentially, compounds according to the present invention include those compounds, which comprise a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c.

A further object of the present invention is a method of using a compound having a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, as an integral part of the compound's overall structure in the manufacture of a pharmaceutical composition for the treatment of disorders of the central nervous system or, particularly, cancer by effective inhibiting of PDE 10.

A further object of the present invention is a method for treating disorders of the central nervous system and/or, particularly, cancer by effective inhibiting of PDE10 comprising administering to a subject in need thereof a pharmaceutically effective and tolerable amount of a compound having a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, particularly, in the subobjects thereto, as an integral part of its overall structure.

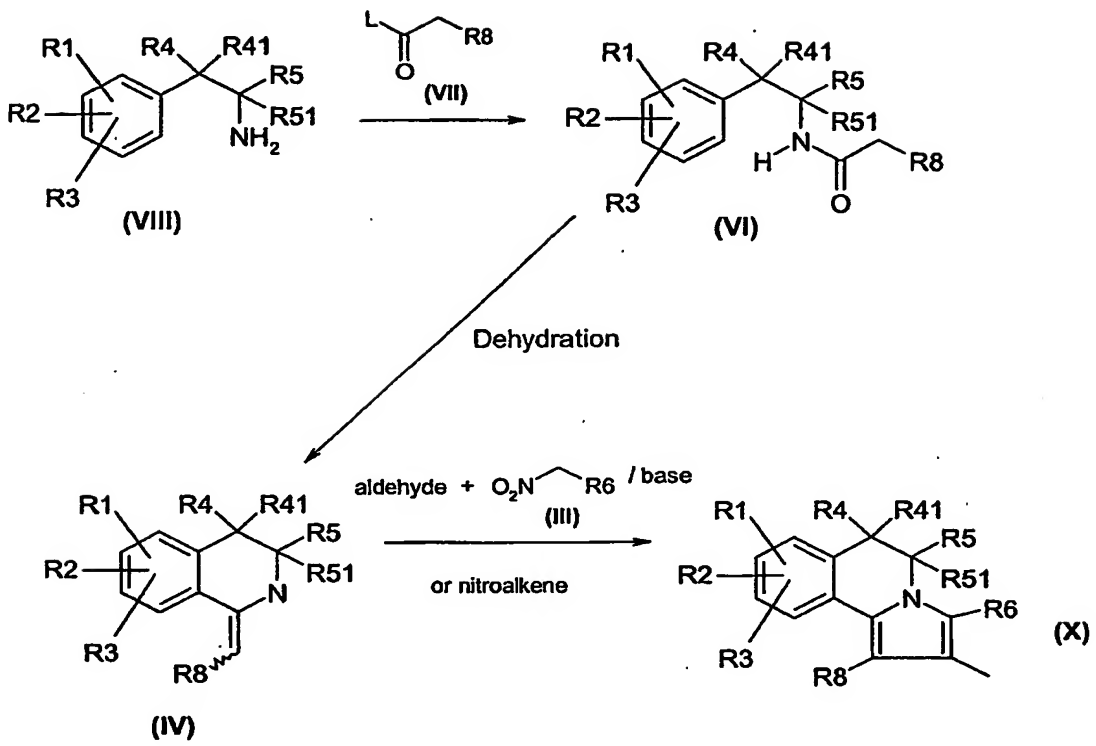
A further object of the present invention is a process or method for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous pharmacological properties (e.g. improved effectiveness) comprising the following steps:
a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class;
b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, in particular, in the subobjects thereto, in more particular in the subobjects emphasized above;
c.) synthesizing substantially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

A further object of the present invention is a method for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous properties comprising the following steps:
a.) selecting intellectually a structure of a compound disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117,
preferably a structure of a compound mentioned expressis verbis or individualized by way of example therein,
more preferably a structure of a compound emphasized therein and/or a structure of a compound disclosed therein with advantageous effects (e.g. advantageous PDE10 inhibiting values);
b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, in particular, in the subobjects thereto, in more particular in the subobjects emphasized above;
c.) synthesizing substantially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

A further object of the present invention is a compound obtainable by one of the abovementioned processes or methods for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class with advantageous properties.

A further object of the present invention is a method for treating disorders of the central nervous system and/or, particularly, cancer by effective inhibiting of PDE10 comprising administering to a subject in need thereof a pharmaceutically effective and tolerable amount of a compound obtainable by the process comprising the following steps:
a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class, or, advantageously,
selecting intellectually a structure of a compound disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117,
preferably a structure of a compound mentioned expressis verbis or individualized by way of example therein,
more preferably a structure of a compound emphasized therein and/or a structure of a compound disclosed therein with advantageous effects (e.g. advantageous PDE10 inhibiting values);
b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, in particular, in the subobjects thereto, in more particular in the subobjects emphasized above;
c.) synthesizing substantially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

The compounds which comprise a structure-element of the formula X or Xa, in which R1, R2, R3, R4, R41, R5, R51, R6 and R8 have the meanings given above in the special objects a, b or c, can be prepared, for example, in an art-known manner, or in a manner described and shown as follows, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or as described by way of example in the following examples, or analogously or similarly thereto.



As shown in the scheme above, in a first reaction step compounds of formula VIII, in which R1, R2, R3, R4, R41, R5 and R51 have the meanings indicated above, are reacted with compounds of formula VII, in which R8 has the meanings indicated above and L is a suitable leaving group, for example chlorine or a acyloxy radical (e.g. the R8-CH_2-C(O)-O- radical), to give in the presence of a suitable organic or inorganic base corresponding compounds of formula VI.

Alternatively, compounds of formula VI are also accessible from compounds of formula VIII, in which R1, R2, R3, R4, R41, R5 and R51 have the meanings indicated above, and compounds of formula VII, in which R8 has the meanings indicated above and L is hydroxyl, by reaction with amide bond linking reagents known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, the carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate or O-(benzotriazol-1yl)-N,N,N',N'-tetramthyl-uronium-hexafluorophosphate] and N,N'-carbonyldiimidazole. In the scope of this invention preferred amide bond linking reagents are uronium salts and, particularly, carbodiimides, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Said reactions are carried out under conditions known to the person skilled in the art or as described exemplarily in the following examples.

As shown in the next step, compounds of the formula IV, in which R1, R2, R3, R4, R41, R5, R51 and R8 have the meanings indicated above, can be obtained by cyclocondensation of corresponding compounds of the formula VI. Said cyclocondensation reaction is carried out in a manner habitual per se to the person skilled in the art or as described by way of example in the following examples, according to Bischler-Napieralski (e.g. as described in J. Chem. Soc., 1956, 4280-4282) in the presence of a suitable condensing or dehydrating agent, such as, for example, polyphosphoric acid, phosphorus pentachloride, phosphorus pentoxide or phosphorus oxychloride, in a suitable inert solvent, e.g. in a chlorinated hydrocarbon such as chloroform, or in a cyclic hydrocarbon such as toluene or xylene, or another inert solvent such as acetonitrile, or without further solvent using an excess of condensing agent, at reduced temperature, or at room temperature, or at elevated temperature or at the boiling temperature of the solvent or condensing agent used.

Compounds of formula IV are converted either with suitable aldehydes and compounds of formula III, in which R6 is 1-6C-alkyl or 1-4C-alkyl substituted by 1-4C-alkoxycarbonyl, or with suitable nitroalkenes, optionally in an one pot synthesis and suitably in the presence of an inorganic or organic base (in particular a cyclic amine, e.g. piperidine) into corresponding compounds which comprise a structure-element of the formula X or Xa. Said conversion can be carried out as known to the skilled person or as described in the following examples or analogously or similarly thereto.

Said suitable aldehydes, nitroalkenes and compounds of formulae VIII, VII and III are commercially available or can be obtained in a manner known to the skilled person from his/her expert knowledge and/or from literature.
Suitable nitroalkenes are known or are accessible by reaction of suitable aldehydes with nitro compounds of formula III in the presence of a suitable organic or inorganic base in a manner customary per se to the skilled person.

Compounds obtained can be converted into further compounds, which comprise a structure-element of the formula X or Xa, by methods known to one of ordinary skill in the art. More specifically, for example, from compounds, in which

a.) R8 or R61 are an ester group, the corresponding acids can be obtained by acidic or, particularly, alkaline hydrolysis;
b.) R8 is an ester group, the corresponding reduced forms thereof (e.g. the hydroxymethyl or methyl radicals) can be obtained by selective reduction reactions;
c.) R8 is a hydroxymethyl group obtainable according b.), the corresponding ester or ether derivatives $-CH_2-O-R81$ can be obtained by esterification or etherification reactions;
d.) R8 is an ester or carboxyl group, the corresponding amides can be obtained by amidification reactions;
e.) R6 is 1-4C-alkyl, particularly methyl, the corresponding halogenated, preferably chlorinated, groups can be obtained by halogenation reaction, particularly by reaction with a chlorination reagent such as sulfuryl chloride, thionyl chloride or N-chlorosuccinimide;

f.) R6 is 1-4C-alkyl substituted by halogen obtainable according e.), the corresponding derivatized 1-4C-alkyl radicals substituted by 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612 can be obtained by nucleophilic substitution reactions with suitable nucleophiles;

g.) R6 is 1-4C-alkyl substituted by hydroxyl obtainable according f.), the corresponding derivatized 1-4C-alkyl radicals substituted by 1-4C-alkoxycarbonyl can be obtained by oxidation and esterification reactions under suitable conditions;

h.) R6 is methyl, the corresponding oxidized forms thereof (e.g. the hydroxymethyl or formyl radicals) can be obtained stepwise or directly by selective oxidation reactions (e.g. with the aid of manganese dioxide to obtain the formyl radicals);

i.) R6 is formyl obtainable according h.), the corresponding aminated compounds can be obtained by reductive amination reaction;

j.) R6 is hydroxymethyl obtainable according h.), the corresponding fluorine compounds can be obtained by fluorination reaction;

k.) R6 is methyl, the corresponding amino compounds can be obtained by nitration reaction and subsequential reduction of the nitro compounds obtained.

The methods mentioned under a.) to k.) are expediently carried out analogously to the methods known to the person skilled in the art or as described by way of example in the following examples.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The isolation and purification of the compounds according to the invention, i.e. the compounds with the structure-element of the formula X or Xa, is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

The compounds according to the present invention include suitable salt forms. Suitable salts for compounds according to the invention - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric

acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

Depending on substitution the compounds according to the present invention can be chiral compounds having, for example, chiral centers and/or chiral axes due to hindered rotation about single bonds. The invention therefore includes all conceivable pure diastereomers and pure enantiomers and mixtures thereof in any mixing ratio including the racemates. The diastereomer mixtures can be separated into the individual isomers by chromatographic processes. The enantiomers can be separated in a known manner (e.g. by chromatographic processes on chiral phases or by resolution).

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds of the formula I. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, variations and adaptations to the described invention can be made on the base of the disclosure (e.g. the explicite, implicite or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

The following examples serve to illustrate the invention in greater detail without restricting it. Likewise, further compounds which comprise a structure-element of the formula X or Xa, whose preparation is not explicitly described, can also be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, m.p. stands for melting point, h for hour(s), min for minutes, conc. for concentrated, satd. for saturated, MS for mass spectrum, M for molecular ion.

The compounds mentioned in the examples as well as their salts and stereoisomers are a preferred subject of the invention.

Examples

Final products

1. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,6,6-trimethyl-5,6-dihydro-pyrrolo[2,1-α]isoquinoline-1-carboxylic acid ethyl ester

Analogously to a procedure described by Meyer in Liebigs Ann. Chem. 1981, 9, 1534-1544, (6,7-dimethoxy-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester (compound A8) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford 2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,6,6-trimethyl-5,6-dihydro-pyrrolo[2,1-α]isoquinoline-1-carboxylic acid ethyl ester as a colorless solid of m.p. 200-202 °C. The mass spectrum shows the molecular peak M+H at 464.3 Da.

The following examples (Examples 2-46) can be prepared in analogy to example 1 using the appropriate starting compound selected from the group consisting of the compounds A1 to A19. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If nitro propane or 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-ethyl-5,6-dihydro-pyrollo[2,1-a]isoquinolines and 3-(8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-α]isoquinolin-3-yl)propionic methyl esters, respectively are obtained.

2. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-α]isoquinoline-1-carboxylic acid ethyl ester
   MS (M+H) = 464.1; m.p. = 210 – 213 °C

3. 8,9-Dimethoxy-3,5,5-trimethyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-α]isoquinoline-1-carboxylic acid ethyl ester
   MS (M+H) = 510.4; m.p. = 52 – 56 °C

4. 2-[3-(4-Chloro-phenoxy)-phenyl]-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
   MS (M+H) = 546.2; m.p. = 61 – 64 °C

5. (6RS)-2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,6-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
   MS (M+H) = 450.1; m.p. = 191 – 194 °C

6. 2-(3-Dimethylamino-phenyl)-8,9-dimethoxy-3,5,5-trimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
   MS (M+H) = 463.1; m.p. = 101 – 102 °C

7. (6RS)-8,9-Dimethoxy-3,6-dimethyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 496.0; m.p. = 150 °C

8. 9-(1,1-Difluoro-methoxy)-2-(3-dimethylamino-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 470.8; m.p. = 107 – 110 °C

9. 9-(1,1-Difluoro-methoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 471.8; m.p. = 152 – 155 °C

10. 9-(1,1-Difluoro-methoxy)-8-methoxy-3-methyl-2-(3,4,5-trimethoxy-phenyl)- 5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 517.8; m.p. = 138 – 141 °C

11. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9,10-trimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 466.1; m.p. = 246 – 251 °C

12. 8-(1,1-Difluoro-methoxy)-9-methoxy-3-methyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 517.7; m.p. = 155 °C

13. 8-(1,1-Difluoro-methoxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-9-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 471.7; m.p. = 126 – 128 °C

14. 8-(1,1-Difluoro-methoxy)-2-(3-dimethylamino-phenyl)-9-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 470.7; m.p. = 118 – 120 °C

15. 8,9-(1,1-Difluoro-methylenedioxy)-2-(3-dimethylamino-phenyl)-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 454.8; m.p. = 136 – 139 °C

16. 8,9-(1,1-Difluoro-methylenedioxy)-2-(4-hydroxy-3,5-dimethyl-phenyl)-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 455.6; m.p. = 176 – 180 °C

17. 8,9-(1,1-Difluoro-methylenedioxy)-3-methyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 501.7; m.p. = 138 – 141 °C

18. 9-Chloro-2-(4-hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 470.7; m.p. = 118 – 120 °C

19. (5RS)- (4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 450.2; m.p. = 158 – 161 °C

20. 9-Chloro-8-methoxy-3-methyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 485.6; m.p. = 172 – 174 °C

21. 9-Chloro-2-(3-dimethylamino-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 438.9; m.p. = 133 – 135 °C

22. 8-Chloro-2-(4-hydroxy-3,5-dimethyl-phenyl)-9-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 439.7; m.p. = 167 – 169 °C

23. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-9-methoxy-8-(2-methoxy-ethoxy)-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 480.2; m.p. = 169 – 171 °C

24. 9-Methoxy-8-(2-methoxy-ethoxy)-3-methyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 526.0; m.p. = 152 – 154 °C

25. 9-Methoxy-8-(2-methoxy-ethoxy)-3-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 486.2; m.p. = 126 – 128 °C

26. (5RS)-5-Ethyl-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 464.1; m.p. = 164 – 166 °C

27. (5RS)-2-Chloro-5-ethyl-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 454.2; m.p. = 121 – 124 °C

28. (4aRS,8aRS)-cis-2-(4-hydroxy-3,5-dimethyl-phenyl)-10,11-dimethoxy-3-methyl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 490.2; m.p. = 186 – 192 °C

29. (5RS)-3-Ethyl-2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 464.1; m.p. = 188 – 190 °C

30. (5RS)-8,9-Dimethoxy-3,5-dimethyl-2-(3,4,5-trimethoxy-phenyl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 496.0; m.p. = 116 – 118 °C

31. (5RS)-8,9-Dimethoxy-3,5-dimethyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 456.1; m.p. = 184 °C

32. (4aRS,8aRS)-cis-10,11-Dimethoxy-3-methyl-2-naphthalen-1-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 496.1; m.p. = 189 – 191 °C

33. (4aRS,8aRS)-cis-10,11-Dimethoxy-3-methyl-2-quinolin-4-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 497.3; m.p. = 153 – 157 °C

34. (4aR,8aR)-10,11-Dimethoxy-3-methyl-2-quinolin-4-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 497.3; oil

35. (4aR,8aR)-10,11-Dimethoxy-3-methyl-2-naphthalen-1-yl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 496.1; m.p. = 212 – 216 °C

36. (4aR,8aR)-2-(4-Hydroxy-3,5-dimethyl-phenyl)-10,11-dimethoxy-3-methyl-4a,5,6,7,8,8a-hexahydro-pyrrolo[2,1-f]phenanthridine-1-carboxylic acid ethyl ester
MS (M+H) = 490.2; m.p. = 203 – 206 °C

37. (5RS)-5-Ethyl-8,9-dimethoxy-3-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 470.1; oil

38. 9-Fluoro-2-(4-hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 423.6; m.p. = 180 – 182 °C

39. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3-methyl-9-nitro-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 450.7; m.p. = 209 – 211 °C

40. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3,9-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 420.0; m.p. = 179 – 181 °C

41. (5RS)-2-(4-Hydroxy-3,5-dimethyl-phenyl)-7,8,9-trimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 480.0; m.p. = 144 °C

42. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1,5-dicarboxylic acid 1-ethyl 5-methyl ester
MS (M+H) = 494.1; m.p. = 92 – 97 °C

43. 8,9-Dimethoxy-3-(2-methoxycarbonyl-ethyl)-6,6-dimethyl-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 543.4; oil

44. (5RS)-8,9-Dimethoxy-3-(2-methoxycarbonyl-ethyl)-5-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 528.1; m.p. = 56 – 59 °C

45. 2-Benzofuran-3-yl-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 432.9; m.p. = 176 – 178 °C

46. 8,9-Dimethoxy-3-methyl-2-(2-methyl-bezofuran-3-yl)-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester
MS (M+H) = 446.9; m.p. = 188 – 190 °C

47. 9-Amino-2-(4-hydroxy-3,5-dimethyl-phenyl)-8-methoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester

A suspension of 200 mg (4.43 mmol) of 2-(4-hydroxy-3,5-dimethyl-phenyl)-8-methoxy-9-nitro-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester (Example 39) and 100 mg of Pd/C (10 %) catalyst in 30 ml of ethanol is placed into an apparatus parr. The bottle is filled with hydrogen at an initial pressure of 30 psi and shaked during 3 hours. The solution is filtered on celite and washed with ethanol and ethyl acetate. After evaporation of the solvents, the residue is purified by chromatography on silica gel eluting with ethyl acetate/petroleum spirit (5:5) to afford 110 mg (59 %) of the title compound as a beige solid of m.p. 104 – 106 °C. The mass spectrum shows the molecular peak M+H at 420.8 Da.

48. 1-[2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-1-yl]-1-phenyl-methanone

Analogously to the procedure described for Example 1, 2-(6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-1-phenyl-ethanone (compound A20) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford 1-[2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-1-yl]-1-phenyl-methanone as a colorless solid of m.p. 194 – 196 °C. The mass spectrum shows the molecular peak M+H at 467.6 Da.

49. 4-(8,9-Dimethoxy-3-methyl-1-phenyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-2,6-dimethyl-phenol

Analogously to the procedure described for Example 1, 1-benzylidene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (compound A21) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford 4-(8,9-dimethoxy-3-methyl-1-phenyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-2-yl)-2,6-dimethyl-phenol as a colorless solid of m.p. 210 – 214 °C. The mass spectrum shows the molecular peak M+H at 439.6 Da.

50. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrollo[2,1-a]isoquinoline-1-carbonitrile

Analogously to the procedure described for Example 1, (6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile (compound A22) is reacted with nitro ethane and 4-hydroxy-3,5-dimethyl benzaldehyde to afford 2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrollo[2,1-a]isoquinoline-1-carbonitrile as a colorless solid of m.p. 285 – 287 °C. The mass spectrum shows the molecular peak M+H at 388.5 Da.

The following examples (Nos. 51-57) can be prepared in analogy to example 50 using the appropriate starting compound A22 or A23. All aldehydes used are commercially available or can be prepared in analogy to published procedures. If 4-nitro butyric acid methyl ester is used instead of nitroethane, 3-

(8,9-dimethoxy-5,6-dihydro-pyrrolo[2,1-α]isoquinolin-3-yl)propionic methyl esters, respectively are obtained.

51. 8,9-Dimethoxy-3-methyl-2-naphthalen-1-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 395.2; m.p. = 226 – 229 °C

52. 8,9-Dimethoxy-3-methyl-2-quinolin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 396.3; m.p. = 239 – 243 °C

53. 2-(1H-Indol-3-yl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 384.3; m.p. = 304 – 307 °C

54. 2-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 473.1; m.p. = 250 – 252 °C

55. 8,9-Dimethoxy-3,5-dimethyl-2-pyridin-4-yl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 360.3; m.p. = 253 – 254 °C

56. 3-[1-Cyano-2-(4-hydroxy-3,5-dimethyl)-8,9-dimethoxy-5-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin3-yl]-propionic acid methyl ester
MS (M+H) = 475.2; m.p. = 208 – 209 °C

57. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3,5-dimethyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carbonitrile
MS (M+H) = 403.2; m.p. = 268 – 270 °C

58. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid cyclohexyl amide

To a solution of 190 µl (1.65 mmol) of cyclohexyl amine in 2 ml of toluene at 0 °C is added dropwise 970 µl (1.92 mmol) of a 2.0 M trimethylaluminum solution in toluene. The reaction mixture is stirred at room temperature for 1 hour and a solution of 240 mg (550 µmol) of 2-(4-hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethyl ester (Example 1) dissolved in 4 ml of tetrahydrofurane and 2 ml of toluene is added dropwise. The resulting mixture is stirred in a sealed tube at 110 °C for 16 hours (reaction followed by TLC analysis). The reaction mixture is cooled to room temperature and 5 N aqueous sodium hydroxide solution is added slowly. The mixture is diluted with water and extracted twice with ethyl acetate. The combined organic phases are dried over magnesium sulfate and concentrated. The residue is purified by chromatography on silica gel eluting with ethyl acetate/petroleum spirit (5:5) and then with ethyl acetate to afford 110 mg (41 %) of

the title compound as a white solid of m.p. 273 – 276 °C. The mass spectrum shows the molecular peak M+H at 488.6 Da.

The following examples (Examples 59-67) can be prepared in analogy to Example 58. All amines used are commercially available. If ammonia chloride is used instead of cyclohexyl amine, the free amide is obtained.

59. 1-[2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinolin-1-yl]-1-pyrrollidin-1-yl-methanone
MS (M+H) = 460.6; m.p. = 216 – 218 °C

60. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid isopropylamide
MS (M+H) = 448.9; m.p. = 233 – 235 °C

61. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid dimethylamide
MS (M+H) = 434.5; m.p. = 259 – 261 °C

62. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid methylamide
MS (M+H) = 421.3; m.p. = 281 – 283 °C

63. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid amide
MS (M+H) = 407.2; m.p. = 229 – 231 °C

64. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid phenylamide
MS (M+H) = 482.6; m.p. = 271 – 273 °C

65. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid ethylamide
MS (M+H) = 435.9; m.p. = 242 – 244°C

66. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid sec-butylamide
MS (M+H) = 464; m.p. = 238 – 240°C

67. 2-(4-Hydroxy-3,5-dimethyl-phenyl)-8,9-dimethoxy-3-methyl-5,6-dihydro-pyrrolo[2,1-a]isoquinoline-1-carboxylic acid cyclopropylamide
MS (M+H) = 448.1; m.p. = 254 – 256°C

Starting compounds

A1 [7-Methoxy-6-(2-methoxy-ethoxy)-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
The title compound can be obtained by a Bischler-Napieralski reaction (Ber. 1893, 26, 1903) using N-{2-[4-methoxy-3-(2-methoxy-ethoxy)-phenyl]-ethyl}-malonamic acid ethyl ester (compound B1) as the starting material.
MS (M+H) = 237.2; m.p. = 79 – 81 °C.

The following 3,4-Dihydro-1(2H)-isoquinolinylidene-derivatives A2 to A18 can be prepared according an analogous procedure using the appropriate starting compound selected from the group consisting of the compounds B2 to B18:

A2 (7-Difluoromethoxy-6-methoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A3 (6-Difluoromethoxy-7-methoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A4 (2,2-Difluoro-7,8-dihydro-6H-[1,3]dioxolo[4,5-g]isoquinolin-5-ylidene)-acetic acid ethyl ester
A5 (7-Chloro-6-methoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A6 (6-Chloro-7-methoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A7 (4RS)-(6,7-Dimethoxy-4-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A8 (6,7-Dimethoxy-4,4-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A9 (3RS)-(6,7-Dimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A10 (3RS)-(3-Ethyl-6,7-dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A11 (6,7,8-Trimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A12 ((4aR,10bR)-8,9-Dimethoxy-1,3,4,4a,5,10b-hexyhydro-2H-phenanthridin-6-ylidene)-acetic acid ethyl ester
A13 ((4aRS,10bRS)-cis-8,9-Dimethoxy-1,3,4,4a,5,10b-hexyhydro-2H-phenanthridin-6-ylidene)-acetic acid ethyl ester
A14 (6-Methoxy-7-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A15 (6-Methoxy-7-nitro-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A16 (7-Fluoro-6-methoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A17 1-Ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinolie-3-carboxylic acid methyl ester
A18 (3RS)-(5,6,7-Trimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
A19 (6,7-Dimethoxy-3,3-dimethyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetic acid ethyl ester
The compound A18 is commercially available.
A20 2-(6,7-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-1-phenyl-ethanone
The compound A20 can be prepared analogously to the above-described synthesis of compound A1 using the starting compound B19.

A21 1-Benzylidene-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline
The compound A21 is commercially available.

A22 (6,7-Dimethoxy-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile
The compound A22 can be prepared analogously to the above-described synthesis of compound A1 using the starting compound B20.

A23 (6,7-Dimethoxy-3-methyl-3,4-dihydro-2H-isoquinolin-1-ylidene)-acetonitrile
The compound A23 can be prepared analogously to the above-described synthesis of compound A1 using the starting compound B21.

B1 N-{2-[4-methoxy-3-(2-methoxy-ethoxy)-phenyl]-ethyl}-malonamic acid ethyl ester
N-{2-[4-methoxy-3-(2-methoxy-ethoxy)-phenyl]-ethyl}-malonamic acid ethyl ester can be prepared by a reaction of 2-[4-Methoxy-3-(2-methoxy-ethoxy)-phenyl)-ethylamine (compound C1) with ethyl maloyl chloride in analogy to procedures in the literature (e.g. Benovsky et al., Tetrahedron Lett. 1997, 38, 8475-8478).
MS (M+H) = 340.2; m.p. = 70 °C

The following amides B2 to B18 can be synthesized according an analogous procedure:

B2 N-{2-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-ethyl}-malonamic acid ethyl ester
B3 N-{2-[3-(1,1-Difluoro-methoxy)-4-methoxy-phenyl]-ethyl}-malonamic acid ethyl ester
B4 N-[2-(2,2-Difluoro-benzo[1,3]dioxol-5-yl)-ethyl]-malonamic acid ethyl ester
B5 N-[2-(4-Chloro-3-methoxy-phenyl)-ethyl]-malonamic acid ethyl ester
B6 N-[2-(3-Chloro-4-methoxy-phenyl)-ethyl]-malonamic acid ethyl ester
B7 N-[(RS)-2-(3,4-Dimethoxy-phenyl)-propyl]-malonamic acid ethyl ester
B8 N-[2-(3,4-Dimethoxy-phenyl)-2-methyl-propyl]-malonamic acid ethyl ester
B9 N-[(RS)-2-(3,4-Dimethoxy-phenyl)-1-methyl-ethyl]-malonamic acid ethyl ester
B10 N-[(RS)-1-(3,4-Dimethoxy-benzyl)-propyl]-malonamic acid ethyl ester
B11 N-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-malonamic acid ethyl ester
B12 N-[(1R,2R)-2-(3,4-Dimethoxy-phenyl)-cyclohexyl]-malonamic acid ethyl ester
B13 N-[(1RS,2RS)-cis-2-(3,4-Dimethoxy-phenyl)-cyclohexyl]-malonamic acid ethyl ester
B14 N-[2-(3-Methoxy-4-methyl-phenyl)-ethyl]-malonamic acid ethyl ester
B15 N-[2-(3-Methoxy-4-nitro-phenyl)-ethyl]-malonamic acid ethyl ester
B16 N-[2-(4-Fluoro-3-methoxy-phenyl)-ethyl]-malonamic acid ethyl ester
B17 3-(3,4-Dimethoxy-phenyl)-2-(2-ethoxycarbonyl-ethanoylamino)-propionic acid methyl ester
B18 N-[(RS)-1-Methyl-2-(2,3,4-trimethoxy-phenyl)-ethyl]malonamic acid ethyl ester

B19 N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-oxo-3-phenyl-propionamide
To a solution of 1.10 g (6.07 mmol) of 2-(3,4-dimethoxy-phenyl)-ethylamine in toluene (6 mL) at 0°C is added dropwise 3.78 mL (7.57 mmol) of a trimethylaluminum 2.0 M solution in toluene. The reaction mixture is stirred at room temperature during 1 hour and a solution of 0.53 mL (3.03 mmol) of ethyl benzoylacetate in toluene (4 ml) is added dropwise. The resulting mixture is stirred in a sealed tube at

100°C during 16 hours (reaction followed by TLC analysis). The reaction mixture is cooled to room temperature and 5 N aqueous solution of sodium hydroxide is slowly added. The mixture is diluted with water and extracted twice with ethyl acetate. The combined organic phases are dried over magnesium sulfate and concentrated. The residue is purified by chromatography on silica gel eluting with ethyl acetate to afford 680 mg (68%) of the title compound as a yellow oil. MS (M+H) = 227.7

B20 2-Cyano-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide

A solution of 10.0 g (55.1 mmol) of 2-(3,4-dimethoxy-phenyl)-ethylamine and 9.36 g (82.7 mmol) of ethyl cyano acetate is stirred at 100 °C for 15 h. The mixture is cooled to room temperature. The precipitate is filtered off and recrystallized from ethanol. 9.44 g (38.0 mmol, 60 %) of 2-cyano-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide are obtained as a beige solid.
MS (M+H) = 249.0, m.p. = 113-115 °C.

B21 2-Cyano-N-[2-(3,4-dimethoxy-phenyl)-1-methyl-ethyl]-acetamide

Compound B21 can be prepared analogously to the synthesis of compound B20.

The appropriate starting compounds for the preparation of the compounds B1 to B21 are commercially available, or can be prepared as described below in the synthesis of the compounds C1 to C3 or analogously or similarly thereto, or can be obtained in analogy to published procedures, e.g. the substituted 2-phenethyl amines can be prepared starting from the corresponding benzaldehydes (see also Shepard et al., J. Org. Chem. 1952, 17, 568).

C1 2-[4-Methoxy-3-(2-methoxy-ethoxy)-phenyl)-ethylamine

2-[4-Methoxy-3-(2-methoxy-ethoxy)-phenyl)-ethylamine can be prepared by alkylation of 4-methoxy-3-hydroxy benzaldehyde with 2-bromomethyl ethyl ether (analogous to a procedure by Ashton et al., J. Med. Chem. 1994, 37, 1696-1703), followed by a sequence described by Shepard et al. in J. Org. Chem. 1952, 17, 568.
MS (M+H) = 226.0

C2 2-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-ethylamine

2-[4-(1,1-Difluoro-methoxy)-3-methoxy-phenyl]-ethylamine can be prepared by difluoromethylation of 4-hydroxy-3-methoxy benzaldehyde with chloro difluoro methane according to a procedure published by Amschler et al. (WO97/28131), followed by a sequence described by Shepard et al. in J. Org. Chem. 1952, 17, 568.
MS (M+H) = 217.6

C3 3-[4-(1,1-Difluoro-methoxy)-2-methoxy-phenyl]-ethylamine

3-[4-(1,1-Difluoro-methoxy)-2-methoxy-phenyl]-ethylamine was prepared by difluoromethylation of 3-hydroxy-4-methoxy benzaldehyde with chloro difluoro methane according to a procedure published by

Amschler et al. (WO97/28131), followed by a sequence described by Shepard et al. in J. Org. Chem. 1952, 17, 568.
MS (M+H) = 217.7

Commercial utility

Intracellular levels of the second messengers cAMP and cGMP are regulated by both their rates of synthesis by cyclases and their hydrolysis by phosphodiesterases. Of the 11 phosphodiesterase (PDE) isoenzymes which are presently known, PDE10 was described for the first time in 1999 (Soderling SH, Bayuga SJ, Beavo JA. Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A. Proc Natl Acad Sci U S A. 1999 Jun 8;96(12):7071-6; Fujishige K, Kotera J, Michibata H, Yuasa K, Takebayashi S, Okumura K, Omori K. Cloning and characterization of a novel human phosphodiesterase that hydrolyzes both cAMP and cGMP (PDE10A). J Biol Chem. 1999 Jun 25;274(26):18438-45; Loughney K, Snyder PB, Uher L, Rosman GJ, Ferguson K, Florio VA. Isolation and characterization of PDE10A, a novel human 3', 5'-cyclic nucleotide phosphodiesterase. Gene. 1999 Jun 24;234(1):109-17). The first gene of this new PDE subfamily was designated PDE10A and the first splice variant was described as PDE10A1, according to the current nomenclature. Due to alternative splicing, other splice variants of PDE10A exist and have been described in the subsequent years (Kotera J, Fujishige K, Yuasa K, Omori K. Characterization and phosphorylation of PDE10A2, a novel alternative splice variant of human phosphodiesterase that hydrolyzes cAMP and cGMP. Biochem Biophys Res Commun. 1999 Aug 11;261(3):551-7; Fujishige K, Kotera J, Omori K. Striatum- and testis-specific phosphodiesterase PDE10A isolation and characterization of a rat PDE10A. Eur J Biochem. 1999 Dec;266(3):1118-27; Fujishige K, Kotera J, Yuasa K, Omori K. The human phosphodiesterase PDE10A gene genomic organization and evolutionary relatedness with other PDEs containing GAF domains. Eur J Biochem. 2000 Oct;267(19):5943-51). PDE10A has been described as a cyclic nucleotide phosphodiesterase exhibiting properties of a cAMP PDE and a cAMP-inhibited cGMP PDE. Individual representatives of the PDE10 isoenzyme are characterized by being particularly prominently expressed in specific areas of the brain (striatum, putamen, caudate nucleus, cerebellum, thalamus), in testis, in the thyroid gland, in the pituitary gland, in kidney and in placenta. Increased expression levels in a broad variety of tumor cell lines and tissues, namely of the lung, breast, pancreas, brain, prostate and ovar indicates that PDE10 may play an important role in tumor cell growth and/or survival under conditions of elevated cAMP and/or cGMP generation.

The use of the structure-element according to the present invention as an integral part of the overall structure of compounds, which inhibit PDE10, can be commercially utilized to provide (i.e. e.g. to design and to manufacture) compounds according to the invention having valuable pharmacological and pharmaceutical properties.

Accordingly, the compounds according to the invention have miscellaneous valuable pharmacological properties which make them commercially utilizable. Thus, for example, the compounds according to the invention are inhibitors of PDE isoenzymes. Particularly, the compounds according to the invention are potent PDE10 inhibitors, some of which are apparently selective (by >100 fold) among other PDE isoenzymes, whereby these selective compounds are particularly preferred in the context of the present invention. The compounds according to the invention therefore can be employed as therapeutic agents for the treatment and prophylaxis of diseases in human and veterinary medicine. As selective cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 10 PDE), they are preferably suitable for treating cancer. For the purposes of this invention the expression "cancer" includes solid tumors as well as leukemia, lymphoma and myeloma. Among solid tumors, preferred indications are malignancies of the lung, breast, pancreas, brain, prostate and ovar. In addition, due to their potent and selective PDE10 inhibitory activity, said compounds are of further potential value in treating disorders of the central nervous system, in particular neurologic and psychiatric disorders, for example those mentioned in EP 1250923 and/or, in more particular, psychotic disorders, anxiety disorders, mood disorders or episodes, drug addiction, movement disorders or disorders comprising deficient cognition as a symptom (e.g. dementia, Parkinson's disease or Alzheimer's disease).

The invention further relates to a method for treating mammals, including humans, which/who are suffering from one of the abovementioned diseases and/or disorders. The method is characterized by the fact that a therapeutically effective and pharmacologically tolerated quantity of one or more of the compounds according to the invention is administered to the affected mammal.

The invention further relates to a method for treating mammals, in particular humans, which/who are suffering from one of the abovementioned diseases and/or disorders comprising the step of administering to said ill mammal a pharmaceutically acceptable composition according to the present invention.

The invention furthermore relates to the compounds according to the invention for use in the treatment and/or prophylaxis of diseases, in particular said diseases and/or disorders.

The invention likewise relates to the use of the compounds according to the invention in the manufacture of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of said diseases and/or disorders.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the said diseases and/or disorders, which pharmaceutical compositions comprise one or more of the compounds according to the invention.

The invention furthermore relates to a commercial product which consists of a customary secondary packaging means, a primary packaging means (for example an ampoule or a blister pack) which

contains a pharmaceutical composition, and, if desired, a patient information leaflet, with the pharmaceutical composition exhibiting an antagonistic effect toward type 10 cyclic nucleotide phosphodiesterases (PDE10) and leading to the attenuation of the symptoms of diseases and/or disorders which are associated with type 10 cyclic nucleotide phosphodiesterases, and with reference being made, on the secondary packaging means and/or on the patient information leaflet of the commercial product, to the suitability of the pharmaceutical composition for use in the prophylaxis or treatment of diseases and/or disorders which are associated with type 10 cyclic nucleotide phosphodiesterases, and with the pharmaceutical composition comprising one or more compounds according to this invention. The secondary packaging means, the primary packaging means containing the pharmaceutical composition and the patient information leaflet otherwise correspond to what the skilled person would regard as being the standard for drugs of this nature.

The pharmaceutical compositions according to this invention are produced using methods with which the skilled person is familiar. When employed in pharmaceutical compositions, the compounds according to the invention (= active compounds) are either used as such or, preferably, in combination with suitable pharmaceutical auxiliaries, for example in the form of tablets, coated (e.g. sugar-coated) tablets, capsules, caplets, suppositories, patches (e.g. as TTS), plasters, emulsions, suspensions, gels or solutions, with the content of active compound advantageously being between 0.1 and 95%, and where, by the appropriate choice of the auxiliaries, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar, on the basis of his/her knowledge, with auxiliaries, carriers, diluents, adjuvants or excipients which are suitable to be used for the desired pharmaceutical compositions. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrines).

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, inhalative, oral, nasal, parenteral, topical, transdermal and rectal delivery.

For the treatment of diseases of the respiratory tract, the compounds according to the invention are preferably administered by inhalation, preferably in the form of an aerosol, with the aerosol particles of solid, liquid or mixed composition having a diameter of from 0.5 to 10 µm, advantageously of from 2 to 6 µm.

The aerosol can be produced, for example, using pressure-driven nozzle nebulizers or ultrasonic nebulizers, advantageously, however, using propellant gas-driven metered aerosols or by means of the propellant gas-free use of micronized active compounds from inhalation capsules.

Depending on the inhalation system employed, the administration forms also contain, in addition to the active compounds, the requisite auxiliary substances, for example propellant gases (e.g. Frigen in the case of metered aerosol), surface-active substances, emulsifiers, stabilizers, preservatives, aromatizing agents, fillers (e.g. lactose in the case of powder inhalers) and, where appropriate, additional active compounds.

For the purposes of inhalation, there are available a larger number of appliances which can be used to generate aerosols of optimal particle size and administer them using an inhalation technique which is as appropriate as possible for the patient. In addition to using attachments (spacers and expanders) and pear-shaped containers (e.g. Nebulator® and Volumatic®), and also automatic spray puff releasers (Autohaler®) for metered aerosols, a number of technical solutions are available, particularly in the case of the powder inhalers (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application 0 505 321), which technical solutions can be used to achieve optimal administration of the active compound.

For the treatment of dermatoses, the compounds according to the invention are used, in particular, in the form of drugs which are suitable for topical administration. For producing the drugs, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliary substances and further processed into suitable medicinal formulations. Suitable medicinal formulations which may be mentioned by way of example are powders, emulsions, suspensions, sprays, oils, ointments, greasy ointments, creams, pastes, gels and solutions.

The required dosage of the active compounds according to this invention can vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to about 100 mg/kg body weight, conveniently administered, for example, in divided doses up to four times a day or in retard form.
The optimal dose and manner of administration of the active compounds necessary in each case can easily be determined by any person skilled in the art on the basis of his/her expert knowledge.

Depending upon the particular disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that disease, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

For example, anti-cancer agents and/or other anti-proliferative agents may be combined with the

compounds of this invention to treat cancer. Examples of known anti-cancer agents include, but are not limited to, Gleevec, Herceptin, Rituxan, Adriamycin, Vincristine, Cyclophosphamide and Ifosfamide, 5-Fluorouracil, Topotecan, Doxorubicin, Paclitaxel (Taxol), Interferons, and Platinum derivatives like Cisplatin or Oxaliplatin.
In addition, compounds according to the present invention can be used in radiation therapy.

The person skilled in the art is aware on the base of his/her expert knowledge of the total daily dosage(s) of the additional therapeutic agent(s) present in the compositions of this invention. Said total daily dosage(s) can vary within a wide range.

A further aspect of the present invention is a composition comprising a first active ingredient, which is a compound according to the present invention, and a second active ingredient, which is an art-known anti-cancer agents and/or an art-known anti-proliferative agent, for simultaneous, sequential or separate use in therapy in any order.

A further aspect of the present invention is a commercial package comprising at least one compound according to this invention as active ingredient(s) together with instructions for simultaneous, sequential or separate use with at least one art-known anti-cancer agent and/or at least one art-known anti-proliferative agent.

Biological investigations

Inhibiting the activity of PDE10A
The PDE10A was cloned into pCR2.1-Topo (Invitrogen) via PCR from human whole brain cDNA using primers OZ 353 (5'- ACCATGTTGACAGATGAAAAAGTGAAGGC –3') and OZ 317 (5'-TCAATCTTCAGATGCAGCTGCC –3'). The ORF encoding for the PDE10A was cut with EcoRV and BamHI and subcloned into SmaI and Bgl II of the expression vector pBP9 (Clontech). The encoded protein represents the PDE10A1 (GenBank Acc.-# AB020593) truncated at its N-terminus at aa 14.

The recombinant baculoviruses were prepared by means of homologous recombination in Sf9 insect cells. The expression plasmids were cotransfected with Bac-N-Blue (Invitrogen) or Baculo-Gold DNA (Pharmingen) using a standard protocol (Pharmingen). Wildtype virus-free recombinant virus supernatants were selected using plaque assay methods. After that, high-titre virus supernatants were prepared by amplifying 3 times. PDE10A1 was expressed in Sf21 cells by infecting $2x10^6$ cells/ml with an MOI (multiplicity of infection) between 1 and 10 in serum-free SF900 medium (Life Technologies, Paisley, UK). Cells were cultured at 28°C, typically for 48 hours, after which they were pelleted for 5-10 min at 1000 g and 4°C. In spinner flasks, cells were cultured at a rotational speed of 75 rpm. The SF21 insect cells were resuspended, at a concentration of approx. $1x10^7$ cells/ml, in ice-cold (4°C) homogenization buffer (20 mM Tris, pH 8.2, containing the following additions: 140 mM NaCl, 3.8 mM

KCl, 1 mM EGTA, 1 mM $MgCl_2$, 10 mM β-mercaptoethanol, 2 mM benzamidine, 0.4 mM Pefabloc, 10 µM leupeptin, 10 µM pepstatin A, 5 µM trypsin inhibitor) and disrupted by ultrasonication on ice. The homogenate was then centrifuged for 10 min at 1000 g (4 °C) and the supernatant was stored at -80 °C until subsequent use (see below). The protein content was determined by the Bradford method (BioRad, Munich) using BSA as the standard.

The PDE10A activity was inhibited by said compounds in a modified SPA (scintillation proximity assay) test, supplied by Amersham Pharmacia Biotech (see procedural instructions "Phosphodiesterase [3H]cAMP SPA enzyme assay, code TRKQ 7090"), carried out in 96-well microtitre plates (MTPs). The test volume was 100 µl and contained 20 mM Tris buffer (pH 7.4), 0.1 mg of BSA (bovine serum albumin)/ml, 5 mM Mg^{2+}, 0.5 µM cAMP (including about 50,000 cpm of [3H]cAMP), 1 µl of the respective substance dilution in DMSO and sufficient recombinant PDE10A1 (1000×g supernatant, see above) to ensure that 15-20% of cAMP was converted under said experimental conditions. After a preincubation of 5 min at 37°C, the reaction was started by adding a substrate (cAMP) and the assays were incubated for a further 15 min; after that, they were stopped by adding SPA beads (50 µl). In accordance with the manufacturer's instructions, the SPA beads had previously been resuspended in water and diluted 1:3 (v/v) and added to IBMX (3 mM). After the beads had been sedimented (> 30 min), the MTPs were analyzed in commercially available measuring appliances and the corresponding IC_{50} values of the compounds for the inhibition of PDE10A activity were determined from concentration-effect curves by means of non-linear regression.

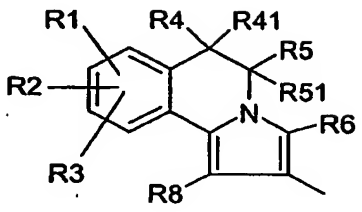
The inhibitory values [inhibitory concentration as $-\log IC_{50}$ (mol/l)] which were determined for the compounds according to the invention are shown in the following table 1, in which the numbers of the compounds correspond to the numbers of the examples.

Table 1: Inhibition of PDE10A activity

Compounds	$-\log IC_{50}$
5, 19, 26, 28, 29, 31, 32, 33, 41, 43, 44, 48, 50, 51, 53, 54 and 55	The inhibitory values of the mentioned Examples lie in the range from 7.04 to 9.24

Patent claims

1. Use of a structure-element of the formula X



(X)

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is hydrogen or 1-4C-alkyl,

R41 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is hydrogen or 1-4C-alkyl,

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl,

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is cyano,

as integral part of the overall structure of compounds which inhibit PDE10.

2. Use of a structure-element of the formula X according to claim 1,

in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy or 3-7C-cycloalkylmethoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy,

R4 is 1-4C-alkyl,

R41 is hydrogen or 1-4C-alkyl,

R5 is hydrogen,

R51 is hydrogen,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkyl,

R51 is hydrogen or 1-4C-alkyl,

or

R4 is hydrogen,

R41 is hydrogen,

R5 is 1-4C-alkoxycarbonyl,

R51 is hydrogen,

or

R4 and R5 together form a 3-4C-alkylene bridge and R41 and R51 are both hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is -C(O)-OR9, in which

R9 is 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

3. Use of a structure-element of the formula X according to claim 1,
in which

R1 is halogen, nitro, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkoxy-2-4C-alkoxy, 3-7C-cycloalkoxy, 3-7C-cycloalkylmethoxy, or completely or predominantly fluorine-substituted 1-4C-alkoxy,

R2 is 1-4C-alkoxy or halogen,

R3 is hydrogen or 1-4C-alkoxy, or

R2 and R3 bound to the benzo ring moiety in ortho-position to each other together form a 1-2C-alkylenedioxy bridge, or

R2 and R3 bound to the benzo ring moiety in ortho-position to each other together form a completely or predominantly fluorine-substituted 1-2C-alkylenedioxy bridge, or

R1 and R2 bound to the benzo ring moiety in ortho-position to each other together form a 1-2C-alkylenedioxy bridge and R3 is hydrogen, or

R1 and R2 bound to the benzo ring moiety in ortho-position to each other together form a completely or predominantly fluorine-substituted 1-2C-alkylenedioxy bridge and R3 is hydrogen,

R4 is hydrogen,

R41 is hydrogen,

R5 is ethyl or, in particular, methyl,

R51 is hydrogen,

R6 is 1-6C-alkyl, amino, formyl, or 1-4C-alkyl substituted by R61, in which

R61 is 1-4C-alkoxycarbonyl, carboxyl, 1-4C-alkoxy, hydroxyl, halogen or -N(R611)R612, in which

R611 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl or 3-7C-cycloalkyl-1-4C-alkyl,

R612 is hydrogen or 1-4C-alkyl, or

R611 and R612 together and with inclusion of the nitrogen atom to which they are bound form a radical Het1, in which

Het1 is a 5- to 7-membered saturated heterocyclic ring radical comprising one nitrogen atom, to which R611 and R612 are bound, and, optionally, one further heteroatom selected from a group consisting of nitrogen, oxygen and sulfur, and optionally substituted by R613 on a ring nitrogen atom, in which

R613 is 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, amino-2-4C-alkyl, mono- or di-1-4C-alkylamino-2-4C-alkyl, formyl, pyridyl or pyrimidinyl,

R8 is 1-4C-alkyl, phenyl, 2-4C-alkinyl, cyano, $-CH_2-O-R81$, phenylcarbonyl, -C(O)-N(R82)R83 or -C(O)-OR9, in which

R81 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4-alkyl or 1-4C-alkylcarbonyl,

R82 is hydrogen, 1-4C-alkyl, 3-7C-cycloalkyl, 3-7C-cycloalkyl-1-4C-alkyl, phenyl or phenyl-1-4C-alkyl,

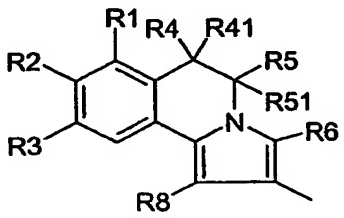
R83 is hydrogen or 1-4C-alkyl, or

R82 and R83 together and with inclusion of the nitrogen atom, to which they are bound, form a heterocyclic ring radical selected from the group consisting of pyrrolidinyl, piperidinyl, morpholinyl or N-(1-4C-alkyl)-piperazinyl,

R9 is hydrogen or 1-4C-alkyl,

as integral part of the overall structure of compounds which inhibit PDE10.

4. Use of a structure-element of the formula Xa



(Xa)

in which

R1 is hydrogen,

R2 is methoxy or ethoxy,

R3 is chlorine or fluorine,

or, as a first alternative,

R1 is hydrogen,

R2 is chlorine or fluorine,

R3 is methoxy or ethoxy,

or, as a second alternative,

R1 is hydrogen,

R2 is methoxy or ethoxy,

R3 is methoxy or ethoxy,

or, as a third alternative,

R1 is methoxy or ethoxy,

R2 is chlorine or fluorine,

R3 is methoxy or ethoxy,

or, as a fourth alternative,

R1 is chlorine or fluorine,

R2 is methoxy or ethoxy,

R3 is methoxy or ethoxy,

or, as a fifth alternative,

R1 is methoxy or ethoxy,

R2 is methoxy or ethoxy,

R3 is chlorine or fluorine,

or, as a sixth alternative,

R1 is methoxy or ethoxy,

R2 is methoxy or ethoxy,

R3 is methoxy or ethoxy,

R4 is hydrogen,

R41 is hydrogen,
R5 is methyl,
R51 is hydrogen,
R6 is methyl, ethyl or methoxycarbonylethyl,
R8 is cyano,
as integral part of the overall structure of compounds which inhibit PDE10.

5. Use of a structure-element of the formula Xa according to claim 4,
in which
R1 is hydrogen,
R2 is methoxy,
R3 is methoxy,
R4 is hydrogen,
R41 is hydrogen,
R5 is methyl,
R51 is hydrogen,
R6 is methyl or methoxycarbonylethyl,
R8 is cyano,
as integral part of the overall structure of compounds which inhibit PDE10.

6. A process to provide compounds, which inhibit PDE10, comprising the following steps:
a.) designing intellectually a structure of a compound comprising - as part of its overall structure - a structure-element of the formula X according to claim 1, 2 or 3, or of the formula Xa according to claim 4 or 5;
b.) synthesizing substantially a compound, which have the structure designed in step a.), in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

7. A process for providing PDE10 inhibitors of the pyrrolodihydroisoquinoline class comprising the following steps:
a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class;
b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure-element of the formula X according to claim 1, 2 or 3, or of the formula Xa according to claim 4 or 5;
c.) synthesizing substantially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

8. A compound obtainable by the process according to claim 6 and/or according to claim 7.

9. A method for treating disorders of the central nervous system and/or cancer by inhibiting of PDE10 comprising administering to a subject in need thereof a pharmaceutically effective and tolerable amount of a compound obtainable by the process comprising the following steps:

a.) selecting intellectually a structure of a compound of the pyrrolodihydroisoquinoline class;

b.) modifying intellectually said selected structure in such a way that the modified structure comprises - as part of its overall structure - a structure-element of the formula X according to claim 1, 2 or 3, or of the formula Xa according to claim 4 or 5;

c.) synthesizing substantially a compound having said modified structure in a manner known to the person skilled in the art, or as disclosed in the specification of the present invention, or as disclosed in WO 02/48144, WO 03/014115, WO 03/014116 or WO 03/014117, or analogously or similarly thereto.

10. A compound, which inhibits PDE10 and which comprises a structure-element of the formula X according to claim 1, 2 or 3, or of the formula Xa according to claim 4 or 5 as an integral part of its overall structure.

Abstract

The invention relates to the use of a certain structure-element as an integral part of the overall structure of pyrrolodihydroisoquinoline compounds, which inhibit PDE10.